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| EXAMINER | |
|---|---|
| CHEN, SHIN LIN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 09/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/634,314 | SAVAKIS ET AL. | |
| | Examiner | Art Unit | |
| | Shin-Lin Chen | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 05 August 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 12-19-03.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The preliminary amendment filed 8-5-03 has been entered. Claims 1-9 are pending and under consideration.

### *Specification*

1. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The phrase "deliver said transposon to said cell population, which cell population stably express the cognate transposase for said transposon" on lines 3 and 4 of the abstract uses the legal phraseology "said". Appropriate correction is required.

2. The disclosure is objected to because of the following informalities: The term "CLAIMS" on page 35 of the specification is improper. Changing the term "CLAIMS" to "We claim:" or "What is claimed is:" would be remedial.

Appropriate correction is required.

3. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in United Kingdom 0102816.6 and 0105642.3 on 2-5-01 and 3-7-01, respectively. It is noted, however, that applicant has not filed a certified copy of those two foreign applications as required by 35 U.S.C. 119(b).

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "a primary culture" in claim 8 is vague and renders the claim indefinite. It is unclear what is "a primary culture". Is the primary culture only the culture medium, or a primary culture of cells, and what kind of cell is intended to? Claim 9 depends from claim 8 but fails to clarify the indefiniteness.

### *Claim Rejections - 35 USC § 112*

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for generating mutations in a population of cells in vitro, does not reasonably provide enablement for generating mutations in a cell population in vivo or generating various transgenic animals having a phenotype for use. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-9 are directed to a method for producing a library of genetic mutations in a cell population by insertional mutagenesis by using a viral vector, such as retroviral, lentiviral, adenoviral and bacculoviral vector, to deliver a transposon, such as Minos, mariner, Hermes and Piggybac transposon, to said cell population, wherein the cell population stably express a regulatable cognate transposase for said transposon and the transposon is mobilized to give rise to the genetic mutations. Claim 2 specifies the population of cells is a transgenic non-human animal. Claims 4 and 5 specify the transposase is under the control of an inducible promoter, such as tetracycline-inducible promoter. Claims 8 and 9 specify the population of cells is an established cell line, a primary culture or a stem cell, such as embryonic stem cell.

The specification states "[t]he cell population may be any suitable cell type, including plant, insect and mammalian cells. The cells may be part of an organisms, in primary culture, or established cell lines. Mammalian cells including (embryonic) stem cells are preferred. The method of the present invention may be used in transgenic organisms, such as transgenic insects, mammals or plants" (p. 8, lines 25-29). Therefore, the claims encompass generating mutations in a cell population in vitro and in vivo, and while generating mutations in a cell population in vivo it includes generating transgenic organisms, such as mammals, insects and plants. The specification only discloses infection of human breast cancer cells MCF7 and T47D, human hepatoma HepG2 cells, and rat embryonic fibroblast Ref1 cells with bacculovirus expressing GFP and integration of Minos transposon into HepG2 chromosome by using BacMilRneo virus and helper BacCMV/ILMi virus. Three transgenic lines were generated by standard procedures carrying the tetO transposase/luciferase cassette (see specification, p. 27-29). The specification fails to provide adequate guidance and evidence for how to generate mutations in a cell

population in vivo by using any viral vector comprising various transposon and/or transposase under the control of various promoters and for how to generate various transgenic organisms, such as mammals, insect, and plants, by using said viral vector, wherein said transgenic organisms has a phenotype for a particular use.

The art of transgenics at the time of the invention held that the resulting phenotype of a transgenic animal was unpredictable at the time of the invention. Kappel et al., 1992 (Current Opinion in Biotechnology, Vol. 3, p. 548-553) reports that the individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct, the site of integration, etc., are the important factors that governs the expression of a transgene (e.g. p. 549)). The genetic background of the transgenic animal has a large impact on the resulting phenotype of the transgenic animal. Sigmund, C., June 2000 (Arterioscler. Thromb. Vasc. Biol., p. 1425-1429), reports that variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene-targeted animals. "Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype" (e.g. abstract). Sigmund further states that "many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studies...Although all mouse strains contain the same collection of genes, it is allelic variation...and the interaction between allelic variants that influence a particular phenotype. These "epigenetic" effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments" (e.g. introduction).

In addition, Houdebine, L-M., 2002 (Journal of Biotechnology, Vol. 98, p. 145-160) points out that reintegration of an isolated gene into the genome of an animal by gene microinjection may generate complex and unpredictable biological situations (e.g. p. 146, first paragraph). Houdebine states that "animal transgenics is still suffering from technical limitations" (e.g. abstract). "Gene replacement by homologous recombination in somatic mammalian cells has relatively poor efficiency and "For unknown reasons, homologous recombination is more frequent in pluripotent embryonic cells" (e.g. p. 148, right column). However, gene transfer or inactivation using embryonic cells has failed in species other than mouse, and "the recombined ES cells have more or less the capacity to participate to the development of chimeric embryos but that transmission of the mutation to progeny has been observed so far only in two mouse lines and essentially of the 129/SV line...The systematic lack of success met in rat, rabbit, chicken, pig, sheep and cow now inclines to consider that the so-called ES cells cannot be used for the germinal transmission of a mutation except in two mouse lines systematic studies to tentatively identify genes involved in the two mouse lines are in course" (e.g. p. 149, left column).

In view of the reasons set forth above, the resulting phenotype of transgenic animals was unpredictable at the time of the invention. No transgenic animals or plants carrying the claimed viral vector comprising a transposon and/or a DNA sequence encoding a transposase has been generated and no phenotype of said transgenic animals or plants has been disclosed in the specification. Therefore, one skilled in the art at the time of the invention would not know how to use the transgenic animals or plants produced by the claimed method and would require undue experimentation to generate the full scope of the claimed transgenic animals and plants, to

determine the phenotype of said transgenic animals and plants, and to determine how to use said transgenic animals and plants.

For the reasons set forth above, one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the full scope of the invention claimed. This is particularly true based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, the level of one of ordinary skill which is high, the amount of experimentation required, and the breadth of the claims.

***Claim Rejections - 35 USC § 102***

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1-4 and 6-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Savakis et al., 1999 (EP0955364 A2, IDS-7).

Claims 1-4 and 6-9 are directed to a method for producing a library of genetic mutations in a cell population by insertional mutagenesis by using a viral vector, such as retroviral, lentiviral, adenoviral and bacculoviral vector, to deliver a transposon, such as Minos, mariner, Hermes and Piggybac transposon, to said cell population, wherein the cell population stably

express a regulatable cognate transposase for said transposon and the transposon is mobilized to give rise to the genetic mutations. Claim 2 specifies the population of cells is a transgenic non-human animal. Claim 4 specifies the transposase is under the control of an inducible promoter. Claims 8 and 9 specify the population of cells is an established cell line, a primary culture or a stem cell, such as embryonic stem cell.

Savakis teaches a method of inducing mutation in a cell or producing a transgenic animal and progeny thereof by introducing an isolated transposable element, such as Minos, and a nucleic acid sequence encoding a transposase protein into a germ line cell, for example embryonic stem cell, of an animal, wherein the transposable element and the nucleic acid sequence encoding the transposase protein are incorporated into a viral vector (e.g. claim 1, 12, [0075], p. 12). Suitable promoters for the expression of a protein encoded by the nucleic acid sequence include SV40 promtoer, human elongation factor (EF-1) promoter, constitutive promoter and regulated promoters, such as heat shock promoters and the cold inducible promoter from B. napus (e.g. [0026] to [0031]). Nucleic acid sequence of interest can be introduced into a mammalian cell using the Minos transposable elements and the modified Minos transposable element containing the nucleic acid of interest can be in a viral vector, and the DNA sequence encoding a transposase protein can be inserted into a viral vector. The viral vectors include retrovirus, adenovirus, parvovirus (adeno-associated virus), and negative strand RNA virus etc. (e.g. [0047], [0049]). Thus, claims 1-4 and 6-9 are anticipated by Savakis.

10. Claims 1-4 and 6-9 are rejected under 35 U.S.C. 102(e) as being anticipated by Savakis et al., May 2001 (US Patent No. 6,225,121 B1, IDS-2).

Claims 1-4 and 6-9 are directed to a method for producing a library of genetic mutations in a cell population by insertional mutagenesis by using a viral vector, such as retroviral, lentiviral, adenoviral and bacculoviral vector, to deliver a transposon, such as Minos, mariner, Hermes and Piggybac transposon, to said cell population, wherein the cell population stably express a regulatable cognate transposase for said transposon and the transposon is mobilized to give rise to the genetic mutations. Claim 2 specifies the population of cells is a transgenic non-human animal. Claim 4 specifies the transposase is under the control of an inducible promoter. Claims 8 and 9 specify the population of cells is an established cell line, a primary culture or a stem cell, such as embryonic stem cell.

Savakis teaches a method of inducing mutation in a cell or producing a transgenic animal and progeny thereof by introducing an isolated transposable element, such as Minos, and a nucleic acid sequence encoding a transposase protein into a cell, wherein the transposable element and the nucleic acid sequence encoding the transposase protein are incorporated into a viral vector (e.g. claim 10, 12, abstract). The cell refers to prokaryotic cell, animal cells and plant cells and can be somatic cells or stem cells. Suitable animal cells can be of invertebrate, mammalian, including human, ovine, porcine, murine (such as embryonic stem cells) etc., or avian origin (e.g. column 9, lines 4-21). Suitable promoters for the expression of a protein encoded by the nucleic acid sequence include SV40 promtoer, human elongation factor (EF-1) promoter, constitutive promoter and regulated promoters, such as heat shock promoters and the cold inducible promoter from B. napus (e.g. column 8). Nucleic acid sequence of interest can be introduced into a mammalian cell using the Minos transposable elements and the modified Minos transposable element containing the nucleic acid of interest can be in a viral vector, and

the DNA sequence encoding a transposase protein can be inserted into a viral vector. The viral vectors include retrovirus, adenovirus, parvovirus (adeno-associated virus), and negative strand RNA virus etc. (e.g. column 11, 12). Thus, claims 1-4 and 6-9 are anticipated by Savakis.

***Claim Rejections - 35 USC § 103***

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bessereau et al., 2000 (WO 00/073510 A1, IDS-5) in view of Savakis et al., 1999 (EP0955364 A2, IDS-7).

Claims 1-9 are directed to a method for producing a library of genetic mutations in a cell population by insertional mutagenesis by using a viral vector, such as retroviral, lentiviral, adenoviral and bacculoviral vector, to deliver a transposon, such as Minos, mariner, Hermes and Piggybac transposon, to said cell population, wherein the cell population stably express a

regulatable cognate transposase for said transposon and the transposon is mobilized to give rise to the genetic mutations. Claim 2 specifies the population of cells is a transgenic non-human animal. Claims 4 and 5 specify the transposase is under the control of an inducible promoter, such as tetracycline-inducible promoter. Claims 8 and 9 specify the population of cells is an established cell line, a primary culture or a stem cell, such as embryonic stem cell.

Bessereau teaches a method of transposon-mediated mutagenesis in a C. elegans genome by introducing a transgene construct comprising a transposase gene under the control of an inducible promter, such as a heat-shock promoter or a tetracycline-regulated promoter, into the C. elegans genome and the expressed transposase cause a transposon in the C. elegans to transpose and cause a mutation, wherein the transposon can be endogenous or heterologous transposon, such as Drosophila mariner element (e.g. abstract, p. 4 lines 18-22, claims 20-27, p. 12 lines 17-29).

Bessereau only teaches using plasmid DNA for mutagenesis but does not teach using viral vector for the introduction of the transposon or DNA sequence encoding transposase into the C. elegans genome.

Savakis teaches a method of inducing mutation in a cell or producing a transgenic animal and progeny thereof by introducing an isolated transposable element, such as Minos, and a nucleic acid sequence encoding a transposase protein into a germ line cell, for example embryonic stem cell, of an animal, wherein the transposable element and the nucleic acid sequence encoding the transposase protein are incorporated into a viral vector (e.g. claim 1, 12, [0075], p. 12). Suitable promoters for the expression of a protein encoded by the nucleic acid sequence include SV40 promtoer, human elongation factor (EF-1) promoter, constitutive

promoter and regulated promoters, such as heat shock promoters and the cold inducible promoter from B. napus (e.g. [0026] to [0031]). Nucleic acid sequence of interest can be introduced into a mammalian cell using the Minos transposable elements and the modified Minos transposable element containing the nucleic acid of interest can be in a viral vector, and the DNA sequence encoding a transposase protein can be inserted into a viral vector. The viral vectors include retrovirus, adenovirus, parvovirus (adeno-associated virus), and negative strand RNA virus etc. (e.g. [0047], [0049]).

It would have been obvious for one of ordinary skill in the art at the time of the invention to use the viral vector comprising the transposon and/or the DNA sequence encoding the tranposase to generate mutations in a cell or in a non-human animal, such as C. elegans because Savakis teaches introducing a viral vector comprising the Minos transposon and/or the DNA sequence encoding a transposase into a cell to induce mutation in said cell or to produce a transgenic animal.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to generate mutations in cells or to produce a transgenic animal as taught by Savakis or to generate mutations in C. elegans genome as taught by Bessereau with reasonable expectation of success.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

**SHIN-LIN CHEN**
**PRIMARY EXAMINER**